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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/524,960	02/18/2005	Julie Kay Bush	X-15582	3556

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EXAMINER	
KOSACK, JOSEPH R	

ART UNIT	PAPER NUMBER
1626	

DATE MAILED: 04/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/524,960	BUSH ET AL.	
	Examiner	Art Unit	
	Joseph Kosack	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,22 and 23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,7 and 22-33* is/are rejected.

7)☒ Claim(s) *2-6 and 8* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/18/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-8 and 26-33 are pending in the instant application.

Priority

The claim to priority as a 371 filing of PCT/US03/23260 filed on August 12, 2003 which claims priority to US Serial Number 60/405,443 filed on August 22, 2002 has been granted in the instant application.

Information Disclosure Statement

The Information Disclosure Statement filed on February 18, 2005 has been considered fully by the Examiner.

Specification

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: Hemihydrate of an M1 Muscarinic Receptor Agonist.

Claim Objections

Claim 6 objected to under 37 CFR 1.75 as being a substantial duplicate of claim 2. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claims 2-6 and 8 objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22-33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement because the specification **while being enabled partially for the treatment of diseases associated with the muscarinic M-1 receptor, such as Alzheimer's disease and schizophrenia** (see Shannon et al., Xanomeline, an M1/M4 preferring muscarinc cholinergic receptor agonist, Schizophrenia Research, 42 (2000), pp. 249-259, especially p. 249) it does not enable one skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims, for the reasons describe below.

As stated in MPEP 2164.01(a), "there are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

The factors to be considered when determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, were described in In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) as:

1. the nature of the invention;
2. the breadth of the claims;
3. the state of the prior art;
4. the relative skill of those in the art;
5. the predictability or unpredictability of the art;
6. the amount of direction or guidance presented [by the inventor];
7. the presence or absence of working examples; and
8. the quantity of experimentation necessary [to make and/or use the invention].

The eight Wands factors are applied to Claims 22-33 of the present invention below:

(1) The Nature of the Invention

Claims 22-33 are directed to methods of treating or prophylactically treating disorders associated with the muscarinic receptors. In particular, claims 22, 24, 26, 28, 30, and 32 claim the method of treating or prophylactically treating any disease associated with muscarinic receptors (Claim 22), cognitive disorders (Claim 24), Alzheimer's disease (Claim 26), schizophrenia (Claim 28), mild cognitive impairment (Claim 30), and cognitive impairment associated with schizophrenia (Claim 32) using the compound of Claim 1, while claims 23, 25, 27, 29, 31, and 33 claim the method of treating or prophylactically treating any disease associated with muscarinic receptors (Claim 23), cognitive disorders (Claim 25), Alzheimer's disease (Claim 27), schizophrenia (Claim 29), mild cognitive impairment (Claim 31), and cognitive

impairment associated with schizophrenia (Claim 33) using the compounds of Claims 2-6.

(2) The Breadth of the claims

Claims 22-33 are directed to methods of antagonizing the muscarinic M-1 receptor, said method comprising administering to a subject an effective amount of the indane derivative compound represented by the compounds of claims 1-6.

Claims 22-33 will be give its broadest reasonable interpretation. The applicable rule for interpreting the claims is that "each claim must be separately analyzed and given its broadest reasonable interpretation in light of and consistent with the written description." See MPEP 2163(II)(1), citing In re Morris, 127 F.3d 1048, 1053-1054; 44 USPQ2d 1023, 1027 (Fed. Cir. 1997). In view of this rule, the diseases listed in Claims 22-33 will be interpreted to encompass the range of symptoms and functions associated with the general definition of the diseases or disorders listed.

(3) The state of the prior art

It was known in the art at the time of this application that the muscarinic receptors play an important role in treating disorders of the central nervous system and other body systems. More specifically, the indane compounds of the present invention are selective agonists of the muscarinic M-1 receptor, wherein the disorder fro treatment is Alzheimer's disease or schizophrenia (see Shannon et al., Xanomeline, an M1/M4 preferring muscarinc cholinergic receptor agonist, Schizophrenia Research, 42 (2000), pp. 249-259, especially p. 249).

The state of the art at the time of this application was that no single compound was known to treat, all five types of muscarinic receptor disorders, M-1 to M-5, or prevent any disorders associated with muscarinic receptors, and all types of cognitive disorders and cognitive impairments. The following are the general definitions of the diseases claimed, and those diseases that would fall under the broad heading of cognitive disorders.

Cognitive disorders/ impairment relate to any disorder where there is a cognitive impairment that doesn't meet the criteria for delirium, dementia, or amnestic disorders. (see www.mental-health-matters.com/disorders <http://www.mental-health-matters.com/disorders>). This is very broad as it could encompass any cognitive impairment, which could include cognitive impairments related to a mental process (ex. beliefs, information processing, etc...) or cognitive impairments related to a biological process (ex. an actual physical manifestation of the disorder). Applicant should provide data within the scope of the instant application that demonstrates that the instantly claimed compound can treat all types of mental and biological cognitive disorders.

Attention Deficit Hyperactivity Disorder (ADHD) is one of the most common mental disorders that develop in children. Children with ADHD have impaired functioning in multiple settings, including home, school, and in relationship with peers. (see <http://www.ninds.nih.gov/disorders>) The patient population that will be treated with the instant compound is unknown. ADHD is a disorder that targets children, while the other disorders target adults. Applicant should provide data within the scope of the instant application, such as patient population data that demonstrates the instantly claimed compound will be effective in children as well as adults.

Mood disorders is a broad condition whereby the prevailing emotional mood is distorted or inappropriate in the circumstances. (see <http://en.wikipedia.org/wiki/Mood_disorder>) There are also two types of mood disorders: depression and bipolar disorder. Depression further encompasses major depression, recurrent depression, psychotic depression, dysthymia, and postpartum depression. Bipolar disorder further encompasses bipolar I, bipolar II, and cyclothymia. Applicant should provide data within the scope of the instant application, that the instantly claimed compound can treat all disorders encompassed within the broad category of mood disorders.

Psychosis is a general term for when rational thought and perception are impaired. (see <http://en.wikipedia.org/wiki/psychosis>) Psychosis is considered to be a symptom of severe mental illness, but not a diagnosis in itself. It is particularly associated with disorders such as schizophrenia. Applicant should provide data within

the scope of the instant application, that the instantly claimed compound can treat psychosis in all disorders that have psychosis as a symptom.

Dementia is not a specific disease. It is a descriptive term for a collection of symptoms that can be caused by a number of disorders that affect the brain. (see <http://www.ninds.nih.gov/disorders>) Applicant should provide data within the scope of the instant application, that the instantly claimed compound can treat dementia in all disorders that have dementia as a symptom.

Parkinson's Disease belongs to a group of conditions called motor system disorders, which are a result of the loss of dopamine-producing brain cells. This is a very difficult disease to diagnose and treat accurately. (see <http://www.ninds.nih.gov/disorders>) In view of this, Applicant should provide data within the scope of the instant application, that the instantly claimed compound can treat Parkinson's Disease.

Aphasia is a neurological disorder cause by damage to the portions of the brain that are responsible for language. Aphasia can further be divided into four categories: (1) expressive aphasia, (2) receptive aphasia, (3) anomic or amnesia aphasia, or (4) global aphasia. (see <http://www.ninds.nih.gov/disorders>). Applicant should provide data within the scope of the instant application, that the instantly claimed compound can treat all four types of Aphasia.

Relevant data that would support a method of using the instantly claimed compound for the treatment of the claimed disease include patient population data, in vivo/in vitro data, mechanisms of action of the compound, journal articles, and the like.

(4) The relative skill of those in the art

The level of skill in the art (pharmaceutical chemists, physicians) would be high.

(5) The predictability or unpredictability of the art

It is noted that the pharmaceutical art generally is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement varies inversely with the degree of unpredictability in the factors involved. In re Fisher, 427 F.2d 833, 839. Therefore, the more unpredictable an area, the more specific enablement is needed in order to satisfy the statute. Added to the unpredictability of the art itself is the question whether the activity against the muscarinic receptor by one of the compound of the present invention could be reliably and predictably extrapolated to in vivo activity in patients with all types of cognitive disorders, ADHD, mood disorders, psychosis, dementia, and aphasia claimed, or the prevention of any disease. There is no absolute predictability, even in view of the high level of skill in the art.

(6) The amount of direction or guidance presented (by the inventor)

The specification in the present invention discloses that the muscarinic M-1 receptor play an important role in treating disorders of the central nervous system. There is support that shows the compounds of claims 1-6 acts as a muscarinic M-1 receptor agonist, but there is insufficient guidance in the specification for the role the muscarinic M-1 receptor plays in all types of cognitive disorders, ADHD, mood disorders, psychosis, dementia, and aphasia claimed, or the prevention of any disease.

(7) The presence or absence of working examples

As noted in the previous section, the specification discloses the general role of muscarinic M-1 receptors in treating disorders of the central nervous system. However, the specification has no working examples, such as in vivo or in vitro studies of the role the muscarinic M-1 receptor plays in all types of cognitive disorders, ADHD, mood disorders, psychosis, dementia, and aphasia, and the prevention of any disease. There is also no definitive data regarding the patient population that is targeted by the compounds of claims 1-6.

(8) The quantity of experimentation necessary (to make and/or use the invention)

Given the absence of direction or guidance (or working examples) in the specification for the role of muscarinic M-1 receptor antagonists of the compounds of claims 1-6, it would cause a skilled artisan an undue amount of experimentation to practice this invention to determine which patients with which diseases would benefit from which of the claimed compounds within the scope of the invention with a reasonable expectation of success.

As stated earlier, the guidance provided in the specification about the role of the muscarinic M-1 receptor agonist in the treatment of certain central nervous system disorders along with the state of the art at the time of the application is insufficient to enable one skilled in the art to practice this invention without an undue amount of experimentation.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the

unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 7, 22-33 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 12, 14, and 16-20 of copending Application No. 10/488,519, now US PGPUB 20040242584 A1 in light of the teachings of SmithKline Beecham Corp. v. Apotex Corp. (403 F.3d 1331, 1343-44, 74 USPQ2d 1398, 1406-07 (Fed. Cir. 2005)).

The instant application teaches the hemihydrate of biphenyl-4-carboxylic acid (R)-(6-(1-[(4-fluorobenzyl)methylamino]ethylideneamino)-2(R)-hydroxyindan-1-yl)amide, its pharmaceutical compositon, and its methods of use to treat or prevent all diseases associated with muscarinic receptors and certain claimed diseases.

'519 teaches the compound: biphenyl-4-carboxylic acid (R)-(6-(1-[(4-fluorobenzyl)methylamino]ethylideneamino)-2(R)-hydroxyindan-1-yl)amide and its

pharmaceutically acceptable salts along with its pharmaceutical composition, and its methods of use to treat the instantly claimed diseases.

While '519 does not teach the hemihydrate form specifically, SmithKline Beecham Corp. v. Apotex Corp. states a claim to a compound, especially an anhydrous form, "inherently" anticipates the instantly claimed hemihydrate form because practicing the process to manufacture the anhydrous compound "inherently results in at least trace amounts of" the claimed hemihydrate even if the prior art did not discuss or recognize the hemihydrate.

This is a provisional obviousness-type double patenting rejection.

Conclusion

Claims 1, 7, and 22-33 are rejected. Claims 2-6 and 8 are objected to. Claims 2-6 and 8 are free of the art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Kosack whose telephone number is (571)-272-5575. The examiner can normally be reached on M-F 7:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on (571)-272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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